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(54) Title: NON–STEROIDAL AGONIST COMPOUNDS AND THEIR USE IN MALE HORMONE THERAPY

(57) Abstract

The present invention relates to a non steroidal agonist compound having formula (I) where R_1, R_2, and R_3 are the same or different and are a hydrogen, a nitro, a cyano, a carbamoyl, a halogen, a perfluoroalkyl, a haloalkylamido, an isothiocyanate, an azide, a diazocarbonyl, a substituted oxirane, or a β–chloroethylamine; R_4 is a hydrogen, an alkyl, or is joined to R_5; R_5 is a hydrogen, a hydroxy, an alkoxy, an acyloxy, an amino, an alkylamino, a halogen, an alkyl, a haloalkyl, or is joined to R_4; R_6 is a hydrogen, an alkyl, or a haloalkyl; A_1 and A_2 is the same or different, each is a direct link or an alkylene; X_1 is a halogen, an oxygen, a sulfur, a sulphinyl, a sulphonyl, an amino, an alkylimino, or an alkylene; R_7 is a hydrogen, a halogen, an alkoxy, a haloalkoxy, an acyloxy, a haloacyloxy, an aryloxy, a thioalkyl, a thioaryl, an amino, an alkylimino, an alkylamido group, a haloalkylamido group, or a phenyl optionally substituted with a halogen, a nitro group, an alkyl, a haloalkyl, a cyano, a hydroxyl, a carboxylic group, an amino, an alkylamino group, a dialkylamino group, a bisalkylamino group, a haloalkylamino group, a dihaloalkylamino group, a bishaloalkylamino group, an acylamido group, a diacylamido group, an alkylacylamido group, a haloacylamido group, a bis(haloacyl)imido group, or an alkylhaloacylamido group. The present invention further relates to a method of producing the non–steroidal agonist compound, a composition containing the non–steroidal agonist compound, and methods of binding an androgen receptor, suppressing spermatogenesis, and providing hormonal therapy for androgen–dependent conditions.

NON-STEROIDAL AGONIST COMPOUNDS AND
THEIR USE IN MALE HORMONE THERAPY

FIELD OF THE INVENTION

The present invention relates to non-steroidal agonist compounds and their

use in male hormone therapy. More particularly, the present invention relates to a non-

steroidal agonist for the androgen receptor and its use in male hormone therapy.

BACKGROUND OF THE INVENTION

The androgen receptor ("AR") is a ligand-activated transcriptional

regulatory protein that mediates induction of male sexual development and function

through its activity with endogenous androgens. Androgens are generally known as the

male sex hormones. The androgenic hormones are steroids which are produced in the

body by the testis and the cortex of the adrenal gland, or synthesized in the laboratory.

Androgenic steroids play an important role in many physiologic processes, including the

development and maintenance of male sexual characteristics such as muscle and bone

mass, prostate growth, spermatogenesis, and the male hair pattern (Matsumoto,

Endocrinol. Met. Clin. N. Am. 23:857-75 (1994)). The endogenous steroidal androgens

include testosterone and dihydrotestosterone ("DHT"). Testosterone is the principal

steroid secreted by the testes and is the primary circulating androgen found in the plasma

of males. Testosterone is converted to DHT by the enzyme 5α-reductase in many

peripheral tissues. DHT is thus thought to serve as the intracellular mediator for most

androgen actions (Zhou, et al., Molec. Endocrinol. 9:208-18 (1995)). Other steroidal

androgens include esters of testosterone, such as the cypionate, propionate,

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phenylpropionate, cyclopentylpropionate, isocarporate, enanthate, and decanoate esters, and other synthetic androgens such as 7-Methyl-Nortestosterone ("MENT") and its acetate ester (Sundaram et al., "7 Alpha-Methyl-Nortestosterone(MENT): The Optimal Androgen For Male Contraception," Ann. Med., 25:199-205 (1993) ("Sundaram")).

5   Because the AR is involved in male sexual development and function, the AR is a likely target for effecting male contraception or other forms of hormone replacement therapy.

Worldwide population growth and social awareness of family planning have stimulated a great deal of research in contraception. Contraception is a difficult

10   subject under any circumstance. It is fraught with cultural and social stigma, religious implications, and, most certainly, significant health concerns. This situation is only exacerbated when the subject focuses on male contraception. Despite the availability of suitable contraceptive devices, historically, society has looked to women to be responsible for contraceptive decisions and their consequences. Although health concerns

15   over sexually transmitted diseases has made men more aware of the need to develop safe and responsible sexual habits, women still often bear the brunt of contraceptive choice. Women have a number of choices from temporary mechanical devices such as sponges and diaphragms to temporary chemical devices such as spermicides. Women also have at their disposal more permanent options such as physical devices like IUDs and cervical

20   caps as well as more permanent chemical treatments such as birth control pills and subcutaneous implants.

However, to date, the only options available for men include the use of condoms and a vasectomy. Condom use, however is not favored by many men because of the reduced sexual sensitivity, the interruption in sexual spontaneity, and the

25   significant possibility of pregnancy caused by breakage or misuse. Vasectomies are also not favored. If more convenient methods of birth control were available to men, particularly long term methods which required no preparative activity immediately prior to a sexual act, such methods could significantly increase the likelihood that men would take more responsibility for contraception.

30   Despite prolonged research, spermatogenesis remains a poorly understood physiologic process. A number of strategies to interfere with normal hormonal control of spermatogenesis have been employed, including androgens, prostagens, and luteinizing

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hormone releasing hormone ("LHRH") analogs (Wu, "Male Contraception: Current Status and Future Prospects," Clin. Endocrin. 29:443:65 (1988) ("Wu 1988")). Administration of the male sex steroids (e.g., testosterone and its derivatives) has shown particular promise in this regard due to the combined gonadotropin-suppressing and

5   androgen-substituting properties of these compounds (Steinberger et al., "Effect of Chronic Administration of Testosterone Enanthate on Sperm Production and Plasma Testosterone, Follicle Stimulating Hormone, and Luteinizing Hormone Levels: A Preliminary Evaluation of a Possible Male Contraceptive," Fertility and Sterility 28:1320-28 (1977)). Chronic administration of high doses of testosterone completely abolishes

10   sperm production (azoospermia) or reduces it to a very low level (oligospermia). The degree of spermatogenic suppression necessary to produce infertility is not precisely known. However, a recent report by the World Health Organization showed that weekly intramuscular injections of testosterone enanthate result in azoospermia or severe oligospermia (i.e., less than 3 million sperm per ml) and infertility in 98% of men

15   receiving therapy (World Health Organization Task Force on Methods for Regulation of Male Fertility, "Contraceptive Efficacy of Testosterone-Induced Azoospermia and Oligospermia in Normal Men," Fertility and Sterility 65:821-29 (1996)).

The main disadvantages of steroidal male contraceptives lie in their undesirable physicochemical and pharmacokinetic properties. Testosterone is readily

20   absorbed after oral administration, but demonstrates little androgenic effect due to rapid hepatic metabolism prior to reaching the systemic circulation. Rapid absorption and metabolism also preclude the use of testosterone via intramuscular injection.

A variety of testosterone esters have been developed which are more slowly absorbed after intramuscular injection and, thus, result in greater androgenic

25   effect. Testosterone enanthate is the most widely used of these esters. While testosterone enanthate has been valuable in terms of establishing the feasibility of hormonal agents for male contraception, it has several drawbacks, including the need for weekly injections and the presence of supraphysiologic peak levels of testosterone immediately following intramuscular injection (Wu, "Effects of Testosterone Enanthate in Normal Men:

30   Experience From a Multicenter Contraceptive Efficacy Study," Fertility and Sterility 65:626-36 (1996)).

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Steroidal ligands which bind the AR and act as androgens (e.g. testosterone enanthate) or as antiandrogens (e.g. cyproterone acetate) have been known for many years and are used clinically (Wu 1988). Although nonsteroidal antiandrogens are in clinical use for hormone-dependent prostate cancer, nonsteroidal androgens have not been reported. For this reason, research on male contraceptives has focused solely on steroidal compounds. However, data obtained during the development of nonsteroidal antiandrogens suggest that nonsteroidal androgens may be realized. In 1988, Tucker et al., ("Synthesis and Structure-Activity Relationships of 3-Substituted Derivatives of 2-Hydroxypropioanilides," J. Med. Chem. 31:954-59 (1988) ("Tucker 1988a")), using hydroxyflutamide as a lead compound, synthesized a large series of compounds with systematic structural modifications and tested their AR binding affinity and *in vivo* antiandrogenic activity. As a result of these studies, many of the structural elements required for nonsteroidal AR binding have been delineated (Tucker 1988a; Glen et al., "Structure-Activity Relationships Among Nonsteroidal Antiandrogens," Proceedings of the Third SCI-RSC Medicinal Chemistry Symposium, Royal Society of Chemistry: London, p. 345-61 (1986) ("Glen")). Glen showed that the AR binding affinity of a series of hydroxyflutamide analogs was dependent on the presence of an electron deficient aromatic ring separated from the tertiary carbinol by an amide link.

Electron-withdrawing groups presented at the 3- and 4- positions of the anilide ring further enhanced the AR binding affinity, particularly when the 4- substituent was cyano or nitro and the 3-substituent was chloro or trifluoromethyl. Physicochemical studies showed that the dominant conformation in these compounds was that in which the amide NH hydrogen bonds to the OH group, as opposed to that in which OH hydrogen bonds to the amidic carbonyl. This alignment between the NH and OH groups confers a planar geometry to the molecule and additional proton-donor ability to the OH group. It is also thought to play a crucial role in AR interaction of these compounds. This effect is also influenced by the electronic properties of other ring substituents (Glen). Tucker (Tucker 1988a; Tucker et al., "Resolution of Nonsteroidal Antiandrogen 4-Cyano-3-[(4-fluorophenyl) sulfonyl)]-2-hydroxy-2-methyl-3'-(trifluoromethyl)-propionanilide and Determination of the Absolute Configuration of the Active Enantiomer," J. Med. Chem. 31:885-87 (1988) ("Tucker 1988b")) synthesized and evaluated the *in vivo* activity of a series of arylthio derivatives, of which Casodex is an example. An infrared study on two

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representative sulfones showed that the dominant (>95%) conformation in nonpolar

solvents is a structure in which the OH group is bound intramolecularly to a sulfonyl

group oxygen atom (Morris, et al., "Non-Steroidal Antiandrogens: Design of Novel

Compounds Based on an Infrared Study of Dominant Conformation and Hydrogen

5   Bonding Properties of a Series of Anilide Antiandrogens," J. Med. Chem. 34:447-55

(1991)). This suggests that the OH group is not free to participate in AR interactions and

that a different binding mechanism may be operative for these compounds. However, an

NMR study by the same group indicated that the hydrogen bond to the sulfonyl group is

disrupted in proton acceptor solvents, such as the aqueous environment of the AR, and

10   enables the OH group to interact as originally proposed (Tucker 1988a). Teutsch et al.,

"Non-Steroidal Antiandrogens: Synthesis and Biological Profile of High Affinity Ligands

for the Androgen Receptor," J. Steroid Biochem. Molec. Biol. 48:111-19 (1994) recently

reported a series of N-substituted arylthiohydantoin derivatives with AR binding affinities

over 100-fold greater than those reported for flutamide, nilutamide, and Casodex. The

15   planar geometry of these compounds corroborates the significance of this conformation

with regard to AR interaction with nonsteroidal ligands. Casodex, recently given the

generic name bicalutamide, was developed as a result of these studies, and has several

advantages over other antiandrogen therapies (Tucker 1988a; Tucker 1988b). Casodex

has about 2 to 4 times the AR binding affinity of flutamide and nilutamide, greater *in vivo*

20   potency, improved tolerance, a long biological half-life (6 days in man) compatible with

once daily dosing, and is well absorbed after oral administration (Neri, et al., "Effects of a

Novel Non-Steroidal Antiandrogen on Canine Prostatic Hyperplasia," Invest. Urol.

10:123-130 (1972); Furr, A Novel Non-Steroidal Peripherally Selective Antiandrogen.

In: Management of Advanced Cancer of Prostate and Bladder," New York, A.R. Liss,

25   pp. 13-26 (1988); Kennealey, et al., "Use of the Non-Steroidal Antiandrogen Casodex in

Advanced Prostatic Carcinoma," Urol. Clin. N. Am. 18(1):99-110 (1991)).

             In addition to antiandrogens, these studies uncovered a number of

structural analogs demonstrating partial agonist activity. Tucker (1988a) showed that

substitution with a trifluoromethyl 3-substituent apparently resulted in partial agonist

30   activity, and that partial agonist activity was enhanced when the 4-substituent was nitro,

as opposed to cyano. However, it is important to note that the objective of the Tucker

studies was to identify nonsteroidal antiandrogens for treatment of prostate cancer.

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Although several partial agonists were identified, the structural properties required for androgenic activity were not further investigated. In addition, Tucker measured *in vivo* functional activity. As such, a compound which produces potent androgenic effects upon interaction with the AR but is rapidly metabolized would demonstrate poor *in vivo*

5   agonism and, therefore, interfere with the identification of valid structure activity relationships. Thus, the animal model used by Tucker was not designed for and was incapable of identifying compounds with AR agonist activity. Molecular cloning and characterization of the cDNA encoding the AR (Lubahn, et al., "The Human Androgen Receptor: Complementary Deoxyribonucleic Acid Cloning, Sequence Analysis and Gene

10   Expression in Prostate," Molec. Endocr. 2:1265-75 (1988); Chang, et al., "Structural Analysis of Complementary DNA and Amino Acid Sequences of Human and Rat Androgen Receptors," PNAS 85:7211-15 (1988); Trapman, et al., "Cloning, Structure and Expression of a cDNA Encoding the Human Androgen Receptor," Biochem. Biophys. Res. Commun. 153:241-48 (1988)) now permit direct measurement of the

15   functional activity of AR ligands in the absence of potentially confounding pharmacokinetic factors. Also, Tucker utilized racemic mixtures of the compounds of interest for their *in vitro* and *in vivo* experiments. This is of particular significance given a recent report regarding the stereoselective pharmacokinetics of Casodex (McKillop, et al., "Metabolism and Enantioselective Pharmacokinetics of Casodex in Man,"

20   Xenobiotica 23:1241-1253 (1993) ("McKillop")). McKillop showed that the elimination half-life of R-Casodex (4.2 days) was significantly longer than that of the S-enantiomer ($t_{1/2}$=19 hrs) in healthy male volunteers receiving a single oral dose of the racemic mixture. Further, area under the plasma concentration-time profile (AUC) for the R-enantiomer was 130-fold greater than that of S-Casodex, indicating a significant

25   difference in physiologic exposure to the two isomers. Differences in functional activity reported by Tucker 1988a and 1988b did not account for potential stereoselective differences in drug metabolism.

In summary, many of the structural elements and geometry required for nonsteroidal ligand binding to the AR have been determined. However, a significant

30   knowledge gap exists with regard to nonsteroidal agonists, due to the fact that previous studies focused on elucidation of structure-activity relationships for receptor antagonists and used test systems providing potentially misleading results. Studies utilizing

stereochemically pure compounds and more specific measures of functional activity were necessary to elucidate the structure-activity relationship for nonsteroidal agonism.

The present invention is directed toward overcoming these above-noted deficiencies.

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SUMMARY OF THE INVENTION

The present invention relates to a non-steroidal agonist compound having the formula:

10
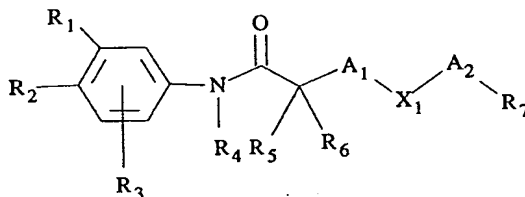
$$R_1, R_2, R_3, N, O, R_4, R_5, R_6, A_1, X_1, A_2, R_7$$

where R_1, R_2 and R_3, are the same or different and are a hydrogen, a nitro, a cyano, a carbamoyl, a halogen, a perfluoroalkyl, a haloalkylamido, an isothiocyanate, an azide, a

15   diazocarbonyl, a substituted oxirane, or a ß-chloroethylamine

R_4 is a hydrogen, an alkyl, or is joined to R_5;

R_5 is a hydrogen, a hydroxy, an alkoxy, an acyloxy, an amino, an alkylamino, a halogen, an alkyl, a haloalkyl, or is joined to R_4;

R_6 is a hydrogen, an alkyl, or a haloalkyl;

20   A_1 and A_2 are the same or different, and each is a direct link or an alkylene;

X_1 is a halogen, an oxygen, a sulfur, a sulphinyl, a sulphonyl, an amino, or an alkylimino, or an alkylene; and

R_7 is a hydrogen, a halogen, an alkoxy, a haloalkoxy, an acyloxy, a

25   haloacyloxy, an aryloxy, a thioalkyl, a thioaryl, an amino, an alkylimino, an alkylamido group, a haloalkylamido group, or a phenyl optionally substituted with a halogen, a nitro group, an alkyl, a haloalkyl, a cyano, a hydroxyl, a carboxylic group, an amino, an alkylamino group, a dialkylamino group, a bisalkylamino group, a haloalkylamino group,

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a dihaloalkylamino group, a bishaloalkylamino group, an acylamido group, a diacylamido group, an alkylacylamido group, a haloacylamido group, a bis(haloacyl)imido group, or an alkylhaloacylamido group.

The present invention also relates to a method of binding a compound to a

5   androgen receptor which includes contacting the androgen receptor with a non-steroidal agonist compound under conditions effective to bind the non-steroidal agonist compound to the androgen receptor.

The present invention also relates to a method of suppressing spermatogenesis in a male patient which includes contacting an androgen receptor of a

10   male patient with a non-steroidal agonist compound under conditions effective to suppress spermatogenesis.

The present invention also relates to a method of hormone therapy which includes contacting an androgen receptor of a patient with a non-steroidal agonist compound under conditions effective to bind the non-steroidal agonist compound to the

15   androgen receptor and effect a change in an androgen-dependent condition.

The present invention also relates to a pharmaceutical composition which includes a non-steroidal agonist compound of the present invention and a pharmaceutically suitable carrier.

Still another aspect of the present relates to a method of producing a non-

20   steroidal AR agonist compound of the present invention.

The novel non-steroidal AR agonists of the present invention, either alone or as a composition, are useful as a male contraceptive or in the treatment of a variety of hormone-related conditions, such as hypogonadism, sarcopenia, erythropoiesis, and osteoporesis. The non-steroidal AR agonists of the present invention offer a significant

25   advance over steroidal androgen treatment because the non-steroidal AR agonists will not be accompanied by serious side effects, inconvenient modes of administration, or high costs. Moreover, the non-steroidal AR agonists offer several advantages; namely, oral bioavailability, lack of cross-reactivity with other steroid receptors, and long biological half-lives.

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DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a non-steroidal agonist compound having

the formula:

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where R_1, R_2, and R_3 are the same or different and are a hydrogen, a nitro, a cyano, a

carbamoyl, a halogen, a perfluoroalkyl, a haloalkylamido, an isothiocyanate, an

10   azide, a diazocarbonyl, a substituted oxirane, or a ß-chloroethylamine;

R_4 is a hydrogen, an alkyl, or is joined to R_5;

R_5 is a hydrogen, a hydroxy, an alkoxy, an acyloxy, an amino, an

alkylamino, a halogen, an alkyl, a haloalkyl, or is joined to R_4;

R_6 is a hydrogen, an alkyl, or a haloalkyl;

15   A_1 and A_2 are the same or different, and each is a direct link or an alkylene;

X_1 is a halogen, an oxygen, a sulfur, a sulphinyl, a sulphonyl, an amino, an

alkylimino, or an alkylene;

R_7 is a hydrogen, a halogen, an alkoxy, a haloalkoxy, an acyloxy, a

haloacyloxy, an aryloxy, a thioalkyl, a thioaryl, an amino, an alkylimino, an alkylamido

20   group, a haloalkylamido group, or a phenyl optionally substituted with a halogen, a nitro

group, an alkyl, a haloalkyl, a cyano, a hydroxyl, a carboxylic group, an amino, an

alkylamino group, a dialkylamino group, a bisalkylamino group, a haloalkylamino group,

a dihaloalkylamino group, a bishaloalkylamino group, an acylamido group, a diacylamido

group, an alkylacylamido group, a haloacylamido group, a bis(haloacyl)imido group, or

25   an alkylhaloacylamido group. The compound binds to an androgen receptor.

The subject invention is best understood through a discussion of receptors

and signal transduction pathways. Cells in higher animals normally communicate by

means of hundreds of kinds of extracellular signaling molecules, including proteins, small

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peptides, amino acids, nucleotides, steroids, retinoids, fatty acid derivatives, and even dissolved gases such as nitric oxide and carbon monoxide. These signaling molecules relay a "signal" to another cell (i.e., a "target cell"), generally affecting a cellular function. As used herein, receptors for extracellular signaling molecules are collectively referred to

5   as "cell signaling receptors".

Many cell signaling receptors are transmembrane proteins on a cell surface; when they bind an extracellular signaling molecule (i.e., a ligand), they become activated so as to generate a cascade of intracellular signals that alter the behavior of the cell. In contrast, in some cases, the receptors are inside the cell and the signaling ligand

10   has to enter the cell to activate them; these signaling molecules therefore must be sufficiently small and hydrophobic to diffuse across the plasma membrane of the cell. As used herein, these receptors are collectively referred to as "intracellular cell signaling receptors".

Steroid hormones are one example of small hydrophobic molecules that

15   diffuse directly across the plasma membrane of target cells and bind to intracellular cell signaling receptors. These receptors are structurally related and constitute the intracellular receptor superfamily (or steroid-hormone receptor superfamily). Steroid hormone receptors include progesterone receptors, estrogen receptors, androgen receptors, glucocorticoid receptors, and mineralocorticoid receptors. The present

20   invention is particularly directed to androgen receptors.

In addition to ligand binding to the receptors, the receptors can be blocked to prevent ligand binding. When a substance binds to a receptor, the three-dimensional structure of the substance fits into a space created by the three-dimensional structure of the receptor in a ball and socket configuration. The better the ball fits into the socket, the

25   more tightly it is held. This phenomenon is called affinity. If the affinity of a substance is greater than the original hormone, it will compete with the hormone and bind the binding site more frequently. Once bound, signals may be sent through the receptor into the cells, causing the cell to respond in some fashion. This is called activation. On activation, the activated receptor then directly regulates the transcription of specific

30   genes. But the substance and the receptor may have certain attributes, other than affinity, in order to activate the cell. Chemical bonds between atoms of the substance and the atoms of the receptors may form. In some cases, this leads to a change in the

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configuration of the receptor, which is enough to begin the activation process (called signal transduction). As a result, substances can be made which bind receptors and activate them (called receptor agonists) or inactivate them (called receptor antagonists).

The present invention is directed to compounds which are agonist

5   compounds, and are, therefore, useful in binding to and activating steroidal hormone receptors. The compounds are non-steroidal. Preferably, the agonist compound of the present invention is an agonist which binds the androgen receptor. Preferably, the compound has high affinity for the androgen receptor. The compound may bind either reversibly or irreversibly to the androgen receptor. The compound of the present

10   invention may contain a functional group (affinity label) that allows alkylation of the androgen receptor (i.e. covalent bond formation). Thus, in this case, the compound binds irreversibly to the receptor and, accordingly, cannot be displaced by a steroid, such as the endogenous ligands dihydrotestosterone and testosterone. It is preferable, however, for the compounds of the present invention reversibly to bind the androgen receptor.

15   Particularly preferred are the non-steroidal agonist compounds below.
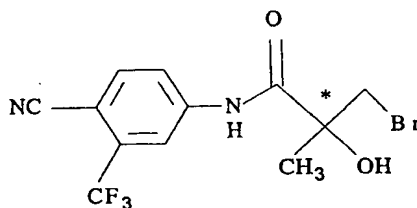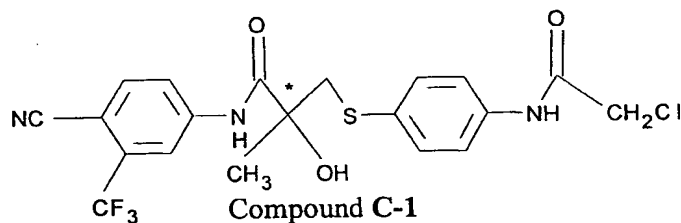
Compound C-1
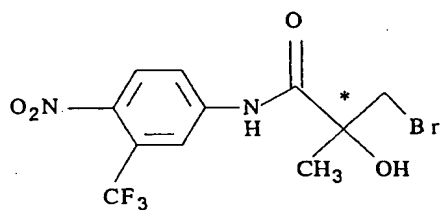
Compound C-2

Compound C-3

Compound C-4

Compound C-5

Compound C-6

-13-

Compound C-7

Compound C-8

Compound C-9

Compound C-10

-14-

Compound C-11
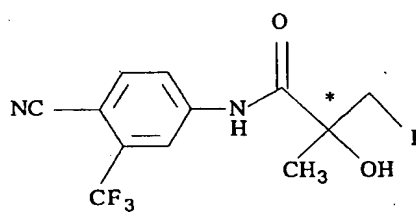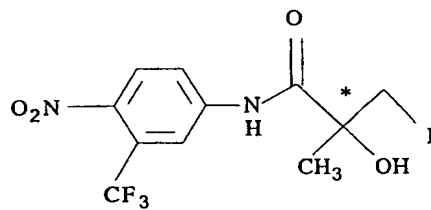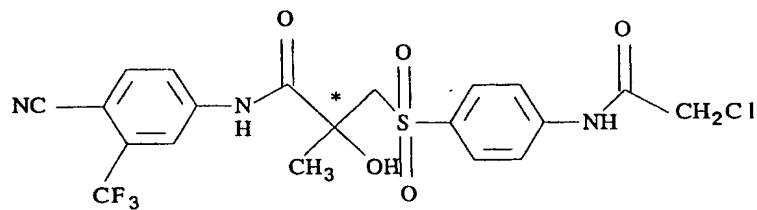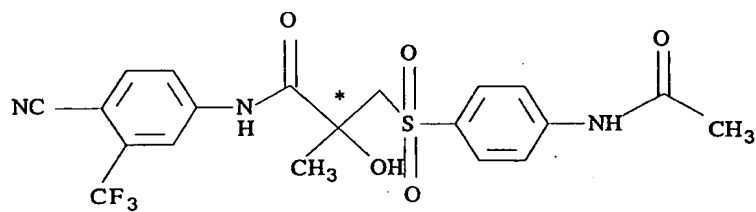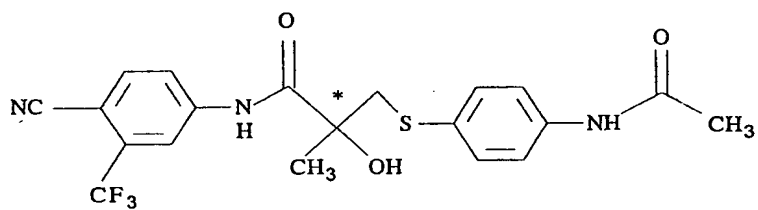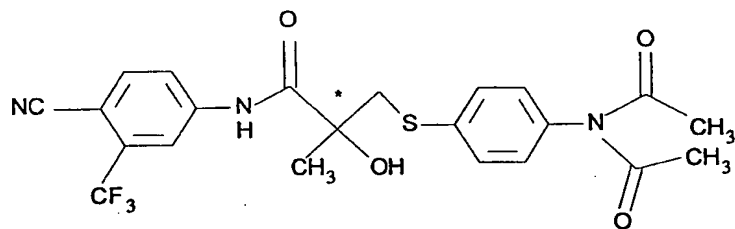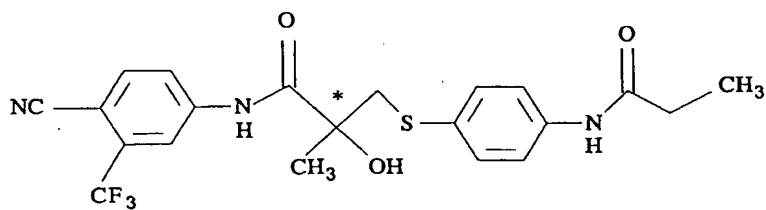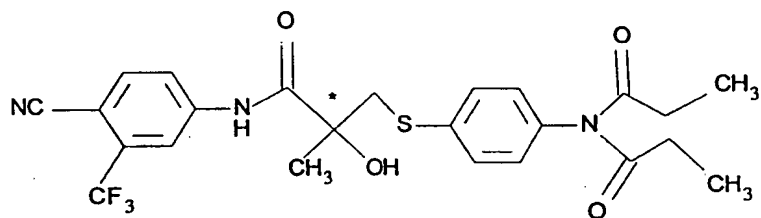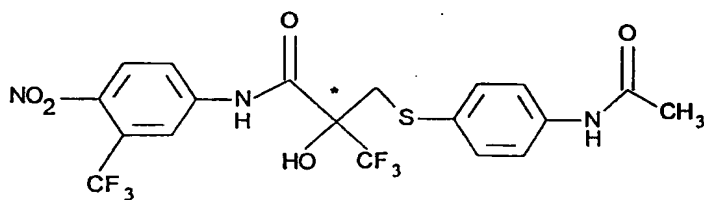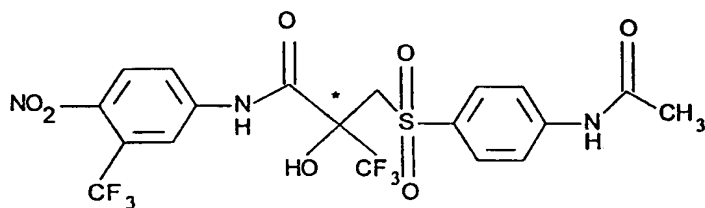

Compound C-12

Compound C-13
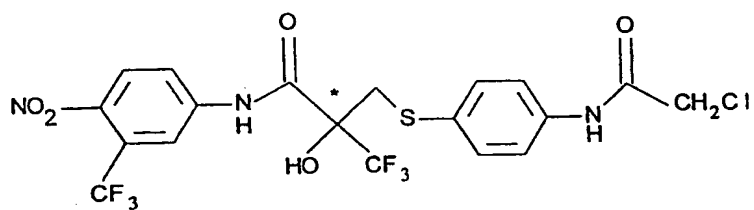
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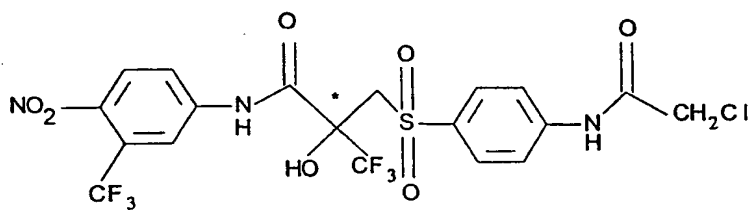
Compound C-15

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The compounds of the present invention include racemic mixtures of the R and S enantiomers. Preferred are substantially pure R and S enantiomers of the compounds. "Substantially pure" is defined herein as greater than about 95% preponderance of one isomer.

5   According to one aspect of the present invention, a method is provided for binding the non-steroidal agonist compounds of the present invention to an androgen receptor by contacting the receptor with a non-steroidal agonist compound under conditions effective to cause the non-steroidal agonist compound to bind the androgen receptor. The binding of the non-steroidal agonist compounds to the androgen receptor

10   enables the compounds of the present invention to be useful as a male contraceptive and in a number of hormone therapies. The agonist compounds bind to and activate the androgen receptor. Binding of the agonist compound is either reversible or irreversible, preferably reversible.

According to one aspect of the present invention, a method is provided for

15   suppressing spermatogenesis by contacting an androgen receptor of a patient with a non-steroidal agonist compound under conditions effective to bind the non-steroidal agonist compound to the androgen receptor and suppress spermatogenesis. Although the exact mechanism by which the non-steroidal agonists of the present invention exert their function is not known, without being bound to any particular theory, it is believed that the

20   non-steroidal agonist compounds of the present invention, by binding to androgen receptors, block the activity of the negative feedback pathway for testosterone regulation. In the negative feedback pathway, elevated testosterone levels in the blood normally causes the pituitary gland to decrease production of luteinizing hormone ("LH") and luteinizing hormone-releasing hormone ("LHRH"), which regulates testosterone

25   production as part of the hypothalamic-pituitary-gonadal axis (Burns-Cox and Gingell, "The Andropause: Fact or Fiction?," Postgrad. Med. J. 73:553-56 (1997), which is hereby incorporated by reference).

According to another aspect of the present invention, a method is provided for hormonal therapy in a patient (i.e., suffering from an androgen-dependent condition)

30   which includes contacting an androgen receptor of a patient with a non-steroidal agonist compound under conditions effective to bind the non-steroidal agonist compound to the androgen receptor and effect a change in an androgen-dependent condition. Androgen-

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dependent conditions which may be treated according to the present invention include those conditions which are associated with aging, such as hypogonadism, sarcopenia, erythropoiesis, osteoporosis, and any other conditions later determined to be dependent upon low androgen (e.g., testosterone) levels. Androgen therapies have been shown to

5   have a positive effect on bone density, muscle mass, red blood cell count and hemoglobin levels, and sexual function. See Swerdloff and Wang, "Androgen Deficiency and Aging in Men," West J. Med. 159:579-85 (1993); Tenover, "Testosterone and the Aging Male," J. Andrology 18(2):103-06 (1997); Burns-Cox and Gingell, "The Andropause: Fact or Fiction?," Postgrad. Med. J. 73:553-56 (1997); Tenover, "Androgen Administration to

10   Aging Men," Clin. Andrology 23:877-92 (1994), which are hereby incorporated by reference.

The compounds herein may be made up in any suitable form appropriate for the desired use; e.g., oral, parenteral (for example, subcutaneously, intravenously, intramuscularly, intraperitoneally, by intranasal instillation, or by application to mucous

15   membranes, such as that of the nose, throat, and bronchial tubes, or by instillation into hollow organ walls or newly vascularized blood vessels) or topical administration. Suitable dosage forms for oral use include tablets, dispersible powders, granules, capsules, suspensions, syrups, and elixirs. The compounds may be administered alone or with suitable pharmaceutical diluents or carriers. Inert diluents and carriers for tablets

20   include, for example, calcium carbonate, sodium carbonate, lactose, and talc. Tablets may also contain granulating and disintegrating agents such as starch and alginic acid, binding agents such as starch, gelatin, and acacia, and lubricating agents such as magnesium stearate, stearic acid, and talc. Tablets may be uncoated or may be coated by known techniques to delay disintegration and absorption. Inert diluents and carriers

25   which may be used in capsules include, for example, calcium carbonate, calcium phosphate, and kaolin. Suspensions, syrups, and elixirs may contain conventional excipients, for example, methyl cellulose, tragacanth, sodium alginate; wetting agents, such as lecithin and polyoxyethylene stearate; and preservatives, e.g., ethyl-p-hydroxybenzoate.

30   Dosage forms suitable for parenteral administration include solutions, suspensions, dispersions, emulsions, and the like. They may also be manufactured in the form of sterile solid compositions which can be dissolved or suspended in sterile

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injectable medium immediately before use. They may contain suspending or dispersing agents known in the art.

It will be appreciated that the actual preferred amount of the compound to be administered according to the present invention will vary according to the particular compound, the particular composition formulated, and the mode of administration. Many factors that may modify the action of the compound can be taken into account by those skilled in the art; e.g., body weight, diet, time of administration, route of administration, rate of excretion, condition of the subject, drug combinations, and reaction sensitivities and severities. Administration can be carried out continuously or periodically within the maximum tolerated dose. Optimal administration rates for a given set of conditions can be ascertained by those skilled in the art using conventional dosage administration tests.

The acylanilides of the invention may be manufactured by any chemical process known to be suitable for the manufacture of chemically-analogous compounds. Examples of suitable chemical processes for manufacturing acylanilides are shown in U.S. Patent No. 4,636,505 to Tucker, which is hereby incorporated by reference. One preferred process for the manufacture of an acylanilide of the invention comprises the reaction of an amine of the formula:
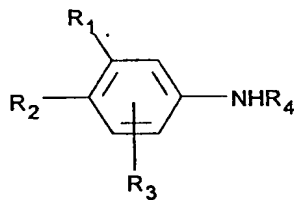
wherein R_1, R_2, R_3, are the same or different, and each is a hydrogen, a nitro, a cyano, a carbamoyl, a halogen, a perfluoroalkyl, a haloalkylamido, an isothiocyanate, an azide, a diazocarbonyl, a substituted oxirane, a ß-chloroethylamine, or other defined and exemplified substituents, and R_4 is a hydrogen, or an alkyl, with an acid of the formula:

$$HO_2C\!-\!CR_5R_6\!-\!A_1\!-\!X_1\!-\!A_2\!-\!R_7$$
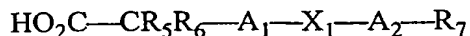
-18-

wherein R_5 is a hydrogen, a hydroxy, an alkoxy, an acyloxy, an amino, an alkylamino, a
halogen, an alkyl, or a haloalkyl; R_6 is a hydrogen, an alkyl, or a haloalkyl; A_1 and A_2 is
the same or different, each is direct link or alkylene; X_1 is a halogen, an oxygen, a sulfur,
a sulphinyl, a sulphonyl, an amino, an alkylimino, or an alkylene; and R_7 is a hydrogen, a

5   halogen, an alkoxy, a haloalkoxy, an acyloxy, a haloacyloxy, an aryloxy, a thioalkyl, a
thioaryl, a sulphinyl, a haloalkyl sulphinyl, a sulphonyl, a haloalkylsulphonyl, an amino,
an alkylimino, an acylamido group, a diacylamido group, a alkylacylamido group, a
haloacylamido group, a haloalkylamino group, an isothiocyanate, an azide, a
diazocarbonyl, a substituted oxirane, a ß-chloroethylamine, or a phenyl optionally

10   substituted with a halogen, a nitro group, an alkyl, a haloalkyl, a cyano, a hydroxyl, a
carboxylic group, an amino, an alkylamino group, a dialkylamino group, a bisalkylamino
group, a haloalkylamino group, a dihaloalkylamino group, a bishaloalkylamino group, an
acylamido group, a diacylamido group, an alkylacylamido group, a haloacylamido group,
a bis(haloacyl)imido group, an alkylhaloacylamido group, an isothiocyanate, an azide, a

15   diazocarbonyl, a substituted oxirane, a ß-chloroethylamine, or with a reactive derivative
of said acid.

         A suitable reactive derivative of an acid is, for example, an acid anhydride,
or an acyl halide, for example an acyl chloride, or a lower alkyl ester of said acid, for
example the methyl or ethyl ester. Preferably the reaction is carried out in N,N-

20   dimethylacetamide solution using an acyl chloride (prepared from the acid and thionyl
chloride) as reactant.

         A second preferred process for the manufacture of an acylanilide of the
invention, wherein R_5 is hydroxy and X_1 is sulphur or alkylimino, comprises the reaction
of an epoxide of the formula:

25
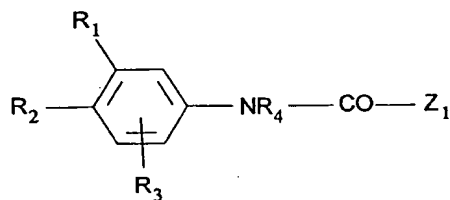
-19-

wherein R_1, R_2, R_3, and R_4 have the meanings stated above and wherein Z_1 has the formula:

$$- CR_6 \overset{O}{\overbrace{}} CHR_{11} \quad or \quad - CR_6OH - CHR_{11}Z_2$$
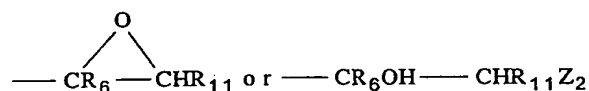
5

wherein R_6 has the meaning stated above, wherein Z_2 is a displaceable group and wherein R_{11} is such that —CHR_{11} is A_1 as stated above, with a thiol or amine of the formula:

$$R_7 - A_2 - SH \text{ or } R_7 - A_2 - NHR_{10}$$

10

wherein R_7 and A_2 have the meanings stated above and R_{10} is an alkyl.

A suitable value for Z_2 is, for example, a halogeno or sulphonyloxy group, for example the chloro, bromo, iodo, methanesulphonyloxy, or p-toluenesulphonyloxy group. The above-mentioned reaction is preferably carried out in an inert diluent or

15   solvent, for example tetrahydrofuran, and in the presence of a base, for example sodium hydride.

The epoxide used as starting material may be obtained by the epoxidation, for example with a base, of the corresponding haloanilide.

A third preferred process for the manufacture of an acylanilide of the

20   invention, wherein R_5 is hydroxy, comprises the reaction of a compound of the formula:

$$R_2 - \overset{\displaystyle R_1}{\underset{\displaystyle R_3}{\bigcirc}} - NR_4 - CO - CO - R_6$$
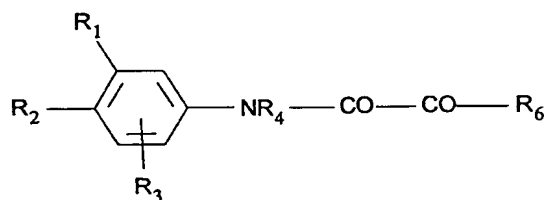
wherein R_1, R_2, R_3, R_4, and R_6 have the meanings stated above, with an organometallic

25   compound of the formula:

-20-

$$R_7—A_2—X_1—A_1—M$$
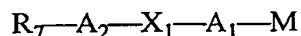
wherein A_1, A_2, R_7, and X_1 have the meanings stated above and M is a metal radical, for example the lithium radical.

The last-mentioned reaction is preferably carried out in an inert solvent, for example diethyl ether or tetrahydrofuran, at a low temperature, for example at between -60°C and -100°C.

An acylanilide of the invention wherein R_4 and R_5 are joined together to form a carbonyloxy group, that is, an oxazolidinedione, may be prepared by the reaction of an isocyanate of the formula:
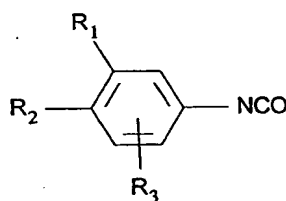
wherein R_1, R_2, and R_3 have the meanings stated above, with an ester of the formula:
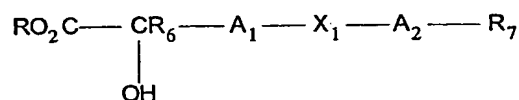
wherein R_6, R_7, X_1, A_1 and A_2 have the meanings stated above, and wherein R is alkyl of up to 6 carbon atoms, for example methyl or ethyl. This reaction is preferably carried out in an organic solvent, for example diethyl ether, at laboratory temperature.

An acylanilide of the invention wherein R_5 is hydroxy may be prepared by the hydrolysis of the corresponding acylanilide wherein R_5 is acyloxy, and an acylanilide of the invention wherein R_5 is hydroxy and R_4 is hydrogen may be prepared by the hydrolysis of the corresponding oxazolidinedione, which may be prepared as described in the preceding paragraph.

An acylanilide of the invention wherein R_4 is alkyl may be prepared by the alkylation of the corresponding acylanilide wherein R_4 is hydrogen.

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An acylanilide of the invention wherein R_5 is acyloxy may be prepared by the acylation of the corresponding acylanilide wherein R_5 is hydroxy.

An oxazolidinedione of the invention, wherein R_4 and R_5 are joined together to form a carbonyloxy group, may be prepared by the reaction of the

5 corresponding acylanilide wherein R_4 is hydrogen and R_5 is hydroxy with phosgene $(COCl_2)$.

An acylanilide of the invention wherein X_1 or X_2 is sulphinyl or sulphonyl or wherein one or more of R_1, R_2, and a substituent in the phenyl or heterocyclic group R_7 is alkylsulphinyl, perfluoroalkylsulphinyl or phenylsulphinyl, or is alkylsulphonyl,

10 perfluoroalkylsulphonyl or phenylsulphonyl, may be prepared by the oxidation of the corresponding acylanilide wherein X_1 or X_2 is sulphur or wherein one or more of R_1, R_2 and a substituent in the phenyl or heterocyclic group R_7, is alkylthio, perfluoroalkylthio or phenylthio. The oxidizing agent and conditions used will determine whether a sulphinyl or a sulphonyl compound is obtained. Thus, oxidation with sodium

15 metaperiodate in methanol solution at or below laboratory temperature will generally convert a thiocompound into the corresponding sulphinyl compound; and oxidation with a per-acid, for example m-chloroperbenzoic acid, in methylene chloride solution at or above laboratory temperature will generally convert a thio compound into the corresponding sulphonyl compound.

20 A fourth preferred process for the manufacture of compounds of the present invention begins with a reaction intermediate having the following formula:
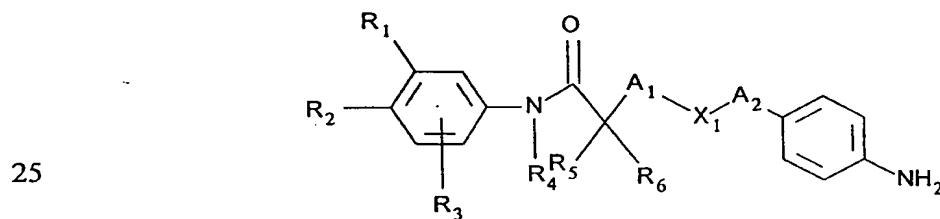
where R_1, R_2, R_3, R_4, R_5, R_6, A_1, A_2, and X_1 have the same meanings as stated above. R_7 is a substituted phenyl group having an amine group at the para- position. The reaction intermediate is reacted with any compound suitable for achieving N-acylation of the amine group. For example, an acyl halide or a haloacyl halide may be used to substitute

30 an acyl group or haloacyl group at R_8 or R_9 to produce the compound below:

-22-
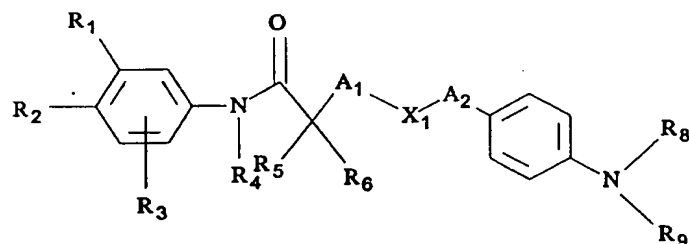
where R_1, R_2, R_3, R_4, R_5, R_6, A_1, A_2, and X_1 have the same meanings as stated above, and R_8 and R_9 are hydrogen, an alcyl group, or a haloacyl group. If desired, the resulting compounds may also be reacted with any compound suitable for achieving sulfonation of the sulfur at X_1, such as peracetic acid.

5   Another preferred process for the manufacture of compounds of the present invention is shown below.

-23-
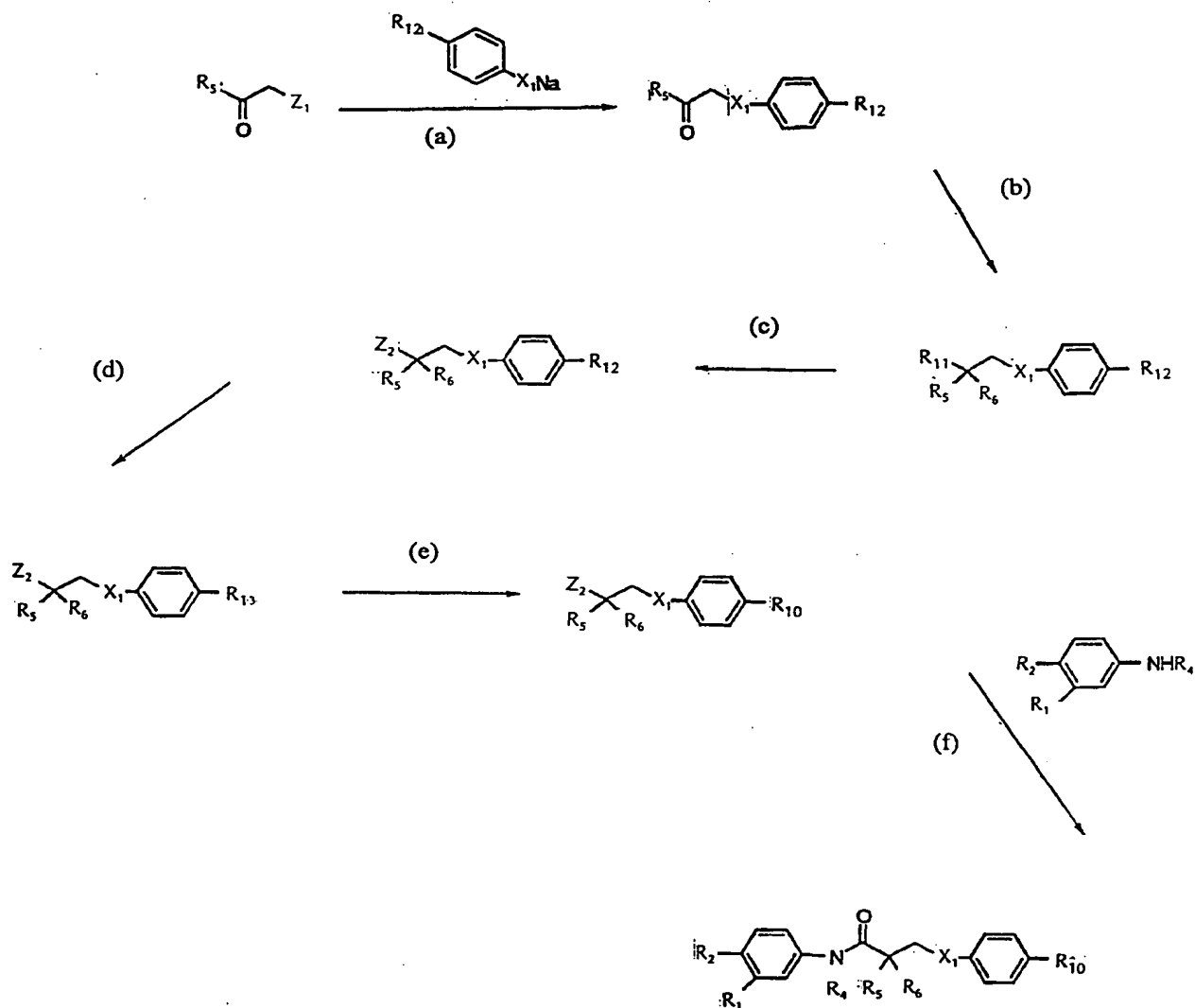
25   where R_1, R_2, R_3, R_4, R_5, R_5, A_1, A_2, and X_1, have the meanings as stated above and R_7 is a
      phenyl substituted with the substituents as described above. Z_1 is any suitable leaving
      group, preferably a halide or a methyl sulfide. Z_2 is any suitable acid, preferably a
      carboxylic acid. R_{10} is an alkylacylamido. R_{11} is any group which can be converted to an
      acid, such as a cyano group. R_{12} is any group which can be converted to an amine,
30   preferably a nitro group. R_{13} is an amine or a substituted amine. The reactions occur
      under conditions effective to produce the desired compounds.

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Depending upon the reaction scheme used to produce the non-steroidal agonist compounds of the present invention, it is possible to produce optically pure isomers. Otherwise, it is desireable to separate R- and S- enantiomers. A racemic

5   acylanilide of the invention wherein R_5 is hydroxy may be separated into its optical isomers by forming an ester of the hydroxy group R_5 with an optically-active acid, for example (—)-camphanic acid, separating the diastereoisomeric esters thus obtained, by fractional crystallization or, preferably, by flash-chromatography, and then hydrolyzing each separate ester to the alcohol. Alternatively, an optically active acylanilide of the

10   invention may be obtained by using any of the processes described above with an optically active starting material. The resulting enantiomer is substantially pure.

EXAMPLES

15   The following examples are provided to illustrate embodiments of the present invention but are by no means intended to limit its scope.

Example 1 - Equilibrium Disassociation Constant and Agonist Activity of Compounds

20   Materials and Methods

Chemicals

(17α-methyl-^{3}H)-Mibolerone (^{3}H-MIB, 83.5 Ci/mmol) and unlabeled MIB

25   were purchased from DuPont Research NEN Products (Boston, MA). Triamcinolone acetonide, phenylmethylsulfonyl fluoride ("PMSF"), TRIS base, sodium molybdate and dithiothreitol were purchased from Sigma Chemical Company (St. Louis, MO). Hydroxyapatite ("HAP") was purchased from BIO-RAD Laboratories (Hercules, CA). EcoLite Plus™ scintillation cocktail was purchased from ICN Research Products

30   Division (Costa Mesa, CA). Dulbecco's modified essential medium ("DMEM") and Lipofectamine™ transfection reagent were purchased from Life Technologies (Gaithersburg, MD). Fetal bovine serum ("FBS") was purchased from Atlanta

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Biologicals, Inc. (Norcross, GA). All materials were used as received from the
manufacturer.

Organic Synthesis

5   R- and S-isomers of compounds C-1 to C-5 were prepared according to

the general synthetic scheme reported for the enantiomers of bicalutamide using

commercially available R-proline (Lancaster Synthesis, Wyndham, NH) as the chiral

auxillary (Mukherjee, et al., Xenobiotica 26:117-22 (1996); Tucker et al., J. Med. Chem.

31:885-87 (1988), which are hereby incorporated by reference). S-isomers were prepared

10   using S-proline as chiral auxillary. The structures of synthesized compounds were in

accordance with the elemental analyses and spectroscopic data (^{1}H and ^{13}C NMR, and

IR).

              R-isomers of compounds C-6 to C-11 were prepared by N-acylation of an

intermediate compound having the structure:

15
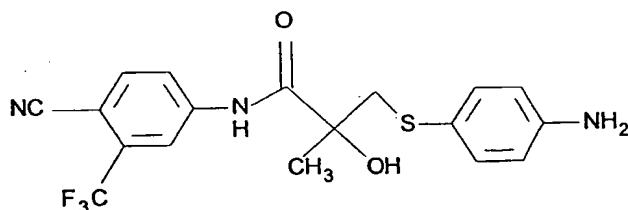
For compounds C-6 and C-7, sulfonation of the sulfur was achieved by treatment with

peracetic acid in ethyl acetate at room temperature.

Preparation of Cytosolic Androgen Receptor

20   Male Sprague-Dawley rats (Harlan Biosciences, Indianapolis, IN),

weighing approximately 250 g, were castrated 24 hours prior to the removal of prostates.

Ventral prostates were surgically removed, weighed, and immersed immediately in an

ice-cold homogenization buffer consisting of 10 mM TRIS, 1.5 mM disodium EDTA, 0.5

mM dithiothreitol, 0.25 M sucrose, 10 mM sodium molybdate, and 1 mM PMSF adjusted

25   to pH 7.2. The prostate tissue (about 0.4 g per rat) was minced, weighed, and

homogenized (Model PRO 200 homogenizer, PRO Scientific, Monroe, CT) with 1 mL of

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the homogenization buffer per 500 mg of prostate tissue. The homogenate was then centrifuged at 114,000 g for 1 hour at 0°C in an ultracentrifuge (Model L8-M, Beckman Instruments Inc., Palo Alto, CA). The supernatant (cytosol) containing AR protein was removed and stored at -80°C until use.

5

Competitive Binding Studies

AR binding affinities of the synthesized ligands were determined by competitive binding in the presence of the high affinity AR ligand, ^{3}H-mibolerone ("[3]H-MIB"). In preliminary experiments, the equilibrium dissociation constant (Kd) of MIB

10   was determined at 4°C for 18 hours by incubating increasing concentrations of ^{3}H-MIB (0.01 to 10 nM) with cytosol. The minimum concentration of ^{3}H-MIB to saturate AR sites in the cytosol preparation was 1 nM. AR binding studies for the ligands of interest were then performed under identical conditions by incubating increasing concentrations (10^{-3} nM to 10,000 nM) of each ligand with cytosol and a saturating concentration of [3]H-

15   MIB (1 nM). The incubate also contained 1 μM triamcinolone to prevent interaction of ^{3}H-MIB with glucocorticoid and progesterone receptors (Carlson and Katzenellenbogen, J. Steroid Biochem. 36:549-61 (1990), which is hereby incorporated by reference). For the determination of non-specific binding, separate experiments were conducted by adding 1,000 nM MIB to the incubate. Unless otherwise indicated, all experiments were

20   repeated three times or more. Separation of bound and free radioactivity at the end of incubation was achieved by the HAP method, as previously described (Mukherjee, et al., Xenobiotica 26:117-22 (1996), which is hereby incorporated by reference), and 0.8 mL of the ethanolic supernatant was added to 5 mL of scintillation cocktail. Radioactivity was counted in a liquid scintillation counter (Model LS6800, Beckman Instruments Inc., Palo

25   Alto, CA).

Data Analysis of AR Binding Affinity

To determine the Kd of MIB, data were analyzed using a modified form of the Scatchard equation:

30

$$B / F = - (B / K_d) + B_{max} / K_d \qquad \text{(Equation 1)}$$

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where B was the concentration of specifically-bound ^{3}H-MIB in the incubate, F was the concentration of free ^{3}H-MIB in the incubate, and B_{max} was the maximum concentration of ^{3}H-MIB specifically bound to AR, which is also the concentration of available AR binding sites in the incubate. Experimental data were computer-fit to equations using fortran subroutines written for PCNONLIN (SCI Software, Lexington, KY).

For competition binding experiments, competitive displacement curves were constructed for each ligand with percent specific binding (specific binding of ^{3}H-MIB at a particular ligand concentration expressed as a percentage of the specific binding of ^{3}H-MIB in the absence of ligand) on the vertical axis and ligand concentration on the horizontal axis. The ligand concentration that reduced the percentage of specific binding by 50% (IC_{50}) was determined by computer-fitting the data for each ligand to the following equation:

$$B = B_0 \{1 - (C / IC_{50} + C)\} \qquad \text{(Equation 2)}$$

where B_0 is the specific binding of ^{3}H-MIB in the absence of ligand, and C is the ligand concentration. Binding affinities of the ligands were then compared using the equilibrium dissociation constant (Ki) of each ligand, as calculated using the equation below:

$$Ki = \{(IC_{50} * Kd)/(L + Kd)\} \qquad \text{(Equation 3)}$$

where Kd was the equilibrium dissociation constant of ^{3}H-MIB as determined in Equation 1, and L was the concentration of ^{3}H-MIB in the incubate (i.e., 1 nM). Low Ki values are associated with agonist activity. The relative binding affinity ("RBA") of each compound was calculated according to the equation below:

$$RBA = \{(IC_{50} \text{ of DHT}) / (IC_{50} \text{ of a ligand})\} * 100\% \qquad \text{(Equation 4)}$$

Transcriptional Activation

The agonist activity of each ligand was examined using transfected CV-1 cells (American Type Culture Collection, Rockville, MD). CV-1 cells were maintained in DMEM containing 10% FBS at 37°C in a humidified atmosphere containing 5% carbon dioxide. DMEM without phenol red was used during transfection studies. One day before transfection, monolayer cells were removed from flasks and plated at a density

-28-

of 4.5 x10^5 cells/well in 6-well tissue culture plates. Cells in each well were then co-transfected with 100 ng of an AR expression vector (plasmid pCMVhAR; provided by Dr. Elizabeth Wilson at The University of North Carolina, Chapel Hill, NC), 2.5 μg of a luciferase reporter vector (plasmid pMMTV-Luc; provided by Dr. Ronald Evans at The

5   Salk Institute, San Diego, CA), and 2.5 μg of a control β-galactosidase vector (plasmid pSV-β-galactosidase; Promega Corporation, Madison, WI). Transfection was performed using Lipofectamine™ according to the manufacturer's instructions (Life Technologies, Gaithersburg, MD). Ten hours after adding the transfection reagent, cells were washed twice with DMEM containing 0.2% FBS and then returned to the incubator. After an

10   additional 10 to 12 hours of incubation, the medium was removed and replaced with DMEM containing 0.2% FBS and various concentrations of DHT or the ligand of interest. Final ligand concentrations were 0.1, 1, 10, 50, 100, 500, and 1,000 nM. The drug-containing medium was replaced after 24 hours of incubation to minimize the possible effects of ligand degradation on measurement of transcriptional activation.

15   Control studies in which neither DHT nor ligand were added to the medium were also performed. Cells were washed with phosphate buffered saline, pH 7.4, after 48 hours of drug treatment and harvested using 350 μL of reporter lysis buffer (Promega Corporation, Madison, WI). Cell lysates were transferred to a microcentrifuge tube, vortexed briefly, and centrifuged at 12,000g for 2 minutes. An aliquot (150 μL) of supernatant was used

20   for determination of β-galactosidase activity in each well using a spectrophotometer (Cary Model 1E, Varian Associates, Sunnyvale, CA) set at a wavelength of 420 nm. A separate aliquot (100 μL) was used for determination of luciferase activity assay (Luciferase Assay System, Promega Corporation, Madison, WI) using an automated luminometer (Model AutoLumat LB953, Wallac Inc., Gaithersburg, MD). Viable cell

25   numbers and transfection efficiency in each well were normalized by expressing the transcriptional activation as a ratio of the luciferase activity to β-galactosidase activity in individual wells. The efficacy of individual compounds compared to DHT was then calculated by dividing (the maximal transcriptional activation observed for each ligand) by (the maximal transcriptional activation observed for DHT). All experiments were

30   performed in triplicate. Potency was reported as the lowest concentration of the ligand used during transfection experiments capable of producing maximal AR-mediated transcriptional activation.

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Results

The values for the equilibrium disassociation constant (Ki) and agonist
activity of the R-isomers of compounds **C-1** through **C-5** are shown in Table 1 below.

5

Table 1

Ligand	Ki (nM)	Agonist Activity[a] (% of DHT)	Potency[b] (nM)
DHT	0.28 ± 0.02	100[d]	1 nM
R-Bicalutamide	11.0 ± 1.5[c]	8.28 ± 2.66	1,000 nM
C-1	1.65 ± 0.10	97.5 ± 21.6	100 nM
C-2	7.98 ± 0.86	18.5 ± 5.08	500 nM
C-3	0.30 ± 0.12	82.9 ± 14.0	500 nM
C-4	2.79 ± 1.35	20.5 ± 7.57	500 nM
C-5	0.86 ± 0.11	88.6 ± 18.0	500 nM

[a] Maximal percentage of transcriptional activation observed for each ligand.
[b] The lowest concentration of the ligand capable of maximally stimulating AR-mediated transcription
during transfection experiments.
[c] Mukherjee, et al., Xenobiotica 26:117-22 (1996).
[d] Ratio of luciferase activity to β-galactosidase activity was 397 ± 144 in the absence of any ligand
(control) and 145,000 ± 33,000 in the presence of 1 nM DHT.

The Kd for ^{3}H-MIB (0.19 ± 0.01 nM; mean ± S.D., n=3) and the binding affinity of DHT
(Table 1) were similar to previously reported values (Mukherjee, et al., Xenobiotica
26:117-22 (1996); Wilson and French, J. Biol. Chem. 251:5620-29 (1976), both of which

10   are hereby incorporated by reference). The Ki of R-bicalutamide was also similar to that
previously reported, and was consistent with the binding affinity of other known
nonsteroidal antiandrogens (Teutsch, et al., J. Steroid Biochem. Molec. Biol. 48:111-19
(1994); Mukherjee, et al., Xenobiotica 26:117-22 (1996); Tucker and Chesterson, J. Med.
Chem. 31:885-87 (1988), all of which are hereby incorporated by reference).

15   Surprisingly, several R-isomers of these analogs bound the AR with
affinity similar to that of DHT, and with much greater affinity than R-bicalutamide (Table
1). Substitution with a chloroacetamido (**C-1**) group at the para-position of the aromatic
ring resulted in a significant increase in AR binding affinity. Likewise, ligands lacking
the sulfonyl moiety and a second aromatic ring (**C-2** to **C-5**) bound the AR with high

20   affinity. Further, it is important to note that this affinity could be increased by replacing
the para-cyano moiety with a nitro- functional group, suggesting that hydrogen bonding at
this position may be critical to interaction with the AR. Further structural modifications

-30-

to introduce the para-nitro substituent in ligands maintaining both aromatic rings (e.g. C-1) may therefore prove useful in identifying additional lead compounds. The equilibrium disassociation constant (Ki value) of the S-isomers of compounds C-1 through C-5 was at least 10-fold greater than the Ki values for R-isomers in all cases. Thus, only the R-

5   isomers of the synthesized analogs were evaluated for their ability to stimulate AR-mediated transcriptional activation.

In all cases, AR-mediated transcriptional activation increased with increasing ligand concentrations and then plateaued at higher concentrations. However, the agonist activity (i.e., maximal degree of AR-mediated transcriptional activation

10   observed) and potency (i.e., the lowest concentration of ligand capable of inducing maximal transcriptional activation) differed greatly between ligands (Table 1). For example, R-bicalutamide, a known antiandrogen, was unable to stimulate AR-mediated transcriptional activation at even the highest concentrations tested (i.e., mean agonist activity of 8.3% at 1,000 nM). Similarly, compounds C-2 and C-4 which lack the

15   sulfonyl moiety and second aromatic ring produced only minimal (<20%) agonist activity. As noted in our studies of AR binding affinity, substitution of a para-nitro functional group significantly increased the degree of agonist activity elicited by this series of ligands (e.g. compare C-2 to C-3 and C-4 to C-5). However, the potency of these compounds was approximately 500-fold lower than that observed with DHT.

20   Structural modifications to include the chloroacetamido- functional group at the para-position (ligand C-1) resulted in the most potent agonist activity. Ligand C-1 demonstrated a mean efficacy of approximately 98% at concentrations as low as 100 nM. Despite the electrophilic character of the chloroacetamido- substituent, studies have shown that this ligand does not covalently (i.e., irreversibly) bind the AR. Another

25   modification to the second aromatic ring includes a ligand incorporating an mono- or di-acetamido- functional group at the para- position.

Example 2 -   Binding Affinity of Compounds

30   Due to the relative binding affinity and equilibrium dissociation constants (Ki) for compound C-1, additional analysis was provided for the compounds listed in the Table 2 below.   Ki and RBA were calculated as described above.

Table 2
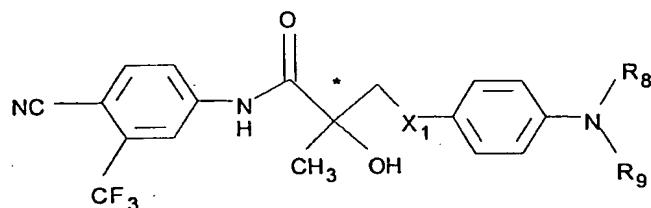
Compound No.	Isomer	X_1	R_8	R_9	RBA (%)	Ki (nM)
C-6	(R)	SO_2	$COCH_2Cl$	H	0.66	40.9
C-7	(R)	SO_2	$COCH_3$	H	15.9	1.70
C-8	(R)	S	$COCH_3$	H	26.9	1.00
C-9	(R)	S	$COCH_3$	$COCH_3$	10.2	2.64
C-10	(R)	S	$COCH_2Me$	H	7.08	3.81
C-11	(R)	S	$COCH_2Me$	$COCH_2Me$	<0.10	>1000
C-1	(R)	S	$COCH_2Cl$	H	17.0	1.65
C-1	(S)	S	$COCH_2Cl$	H	<0.10	>1000
C-8	(S)	S	$COCH_3$	H	0.19	141
DHT					100	

Example 3 -   Synthesis of Compounds

5

(R)- and (S)-enantiomers of compounds of the present invention were
synthesized by mono- or diacylation of the reaction intermediate, as well as sulfonation
thereof. More specifically, non-steroidal agonist compounds **C-1**, **C-6**, **C-10**, and **C-11**
are prepared according to the schemes below.

-32-
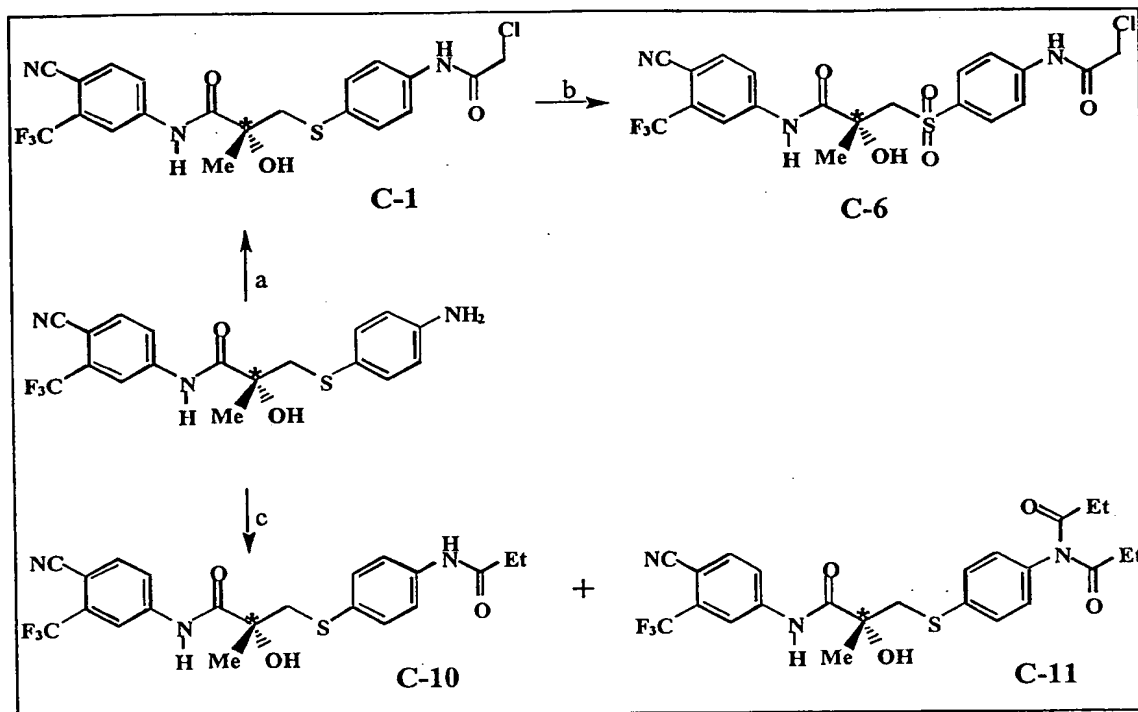
In step (a), the intermediate compound is reacted with $ClCH_2COCl$ in CH_2Cl_2 at room temperature to produce compound **C-1**. In step (b), compound **C-1** is treated with peracetic acid in ethyl acetate at room temperature to form compound **C-6**. In step (c), the intermediate compound is treated with propanoyl bromide (EtCOBr) in CH_2Cl_2 at room temperature to form compounds **C-10** and **C-11**, which are separated from one another by column separation.

In addition, non-steroidal agonist compounds **C-7**, **C-8**, and **C-9** were prepared according to the schemes below.

-33-
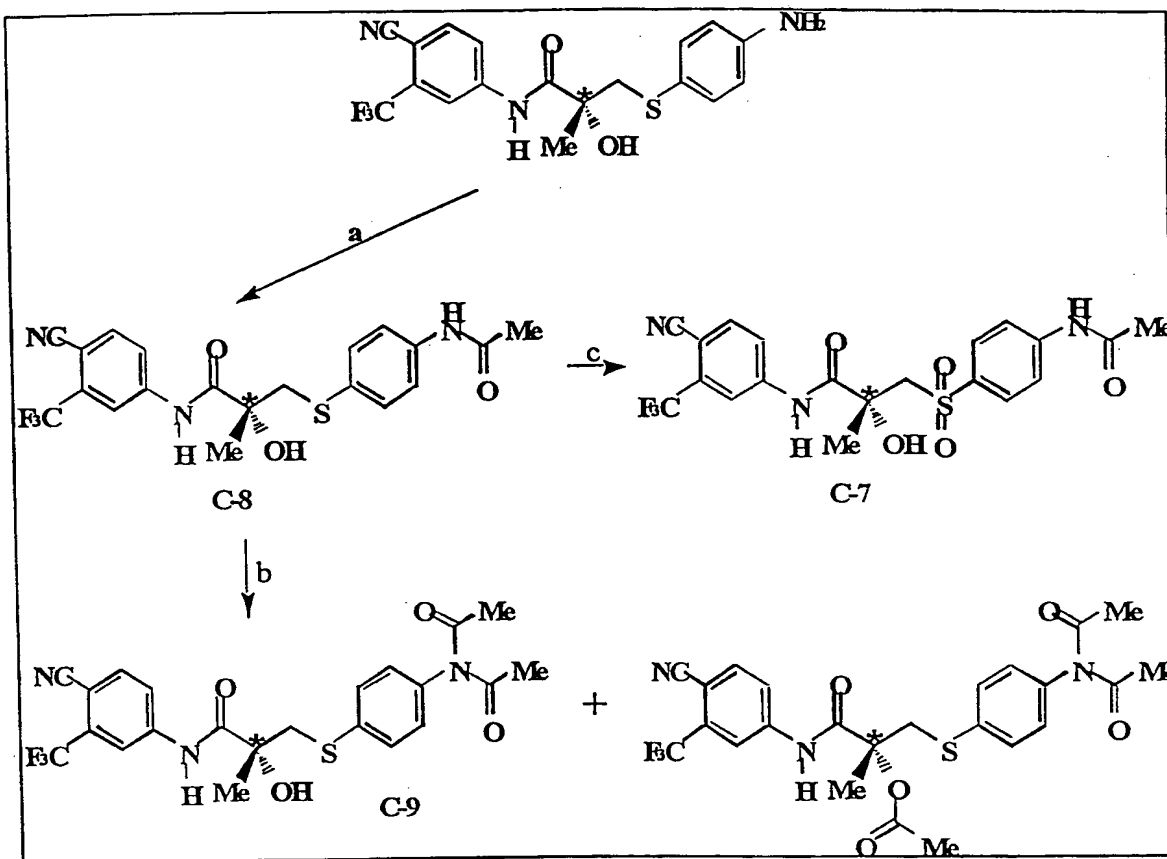
In step (a), the intermediate compound is treated with acid anhydride at room temperature to form compound C-8. In step (b), compound C-8 is treated with acid anhydride to form compound C-9, which is separated from the by-product compound by reflux and column separation. In step (c), compound C-8 is treated with peracetic acid in ethyl acetate at room temperature to yield compound C-7.

Non-steroidal agonist compounds C-12, C-13, C-14, and C-15 were prepared according to the scheme below.

-34-

CH₃COOOH

(g)

C-12
C-14

C-13
C-15
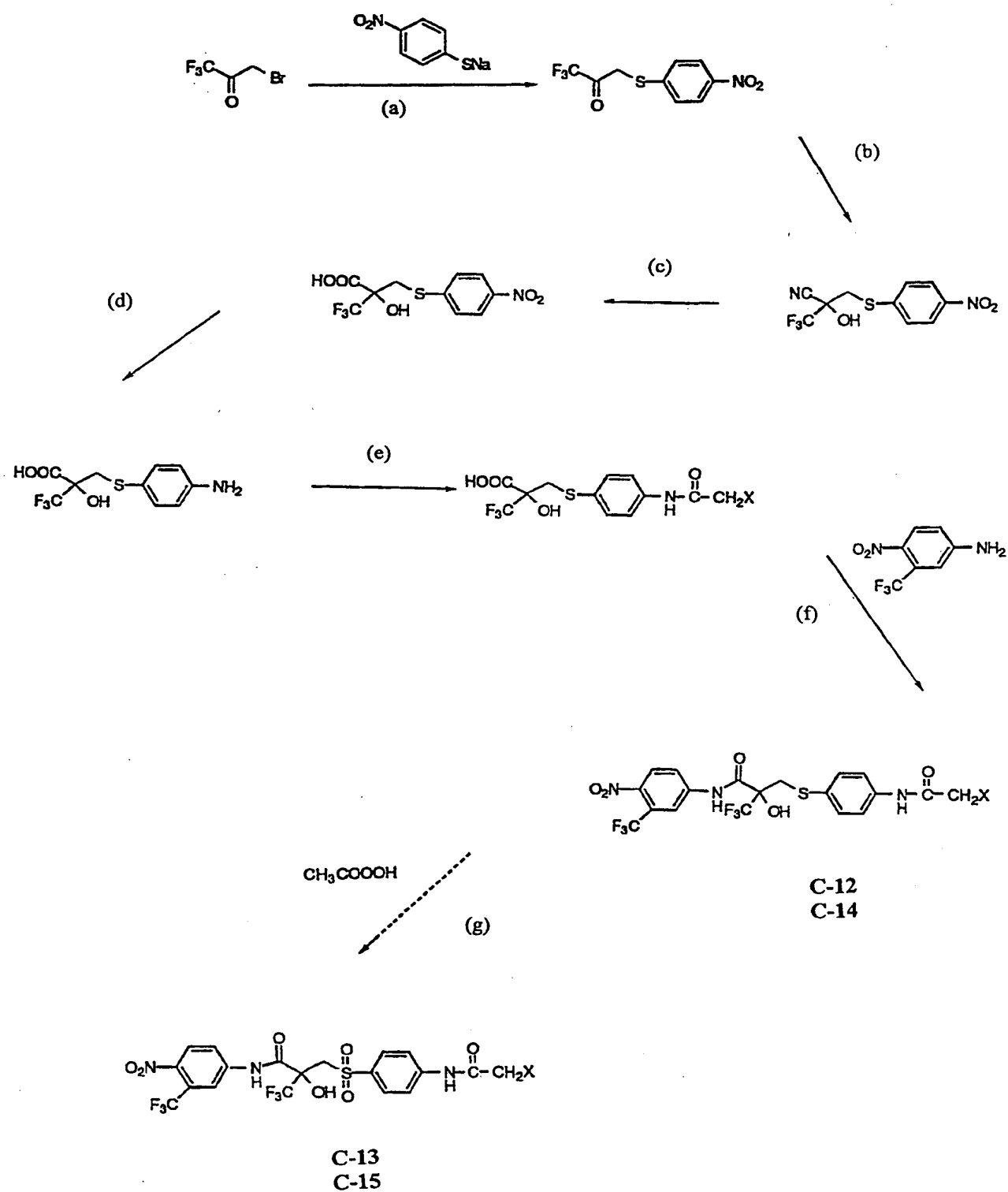
-35-

In step (a), a solution of 4.6 g (26 mmol.) sodium salt of p-nitrothiophenol (prepared according to the procedure of Holt et al. (J. Am. Chem. Soc. 46:2331 (1924), which is hereby incorporated by reference) in 30 mL anhydrous tetrahydrofuran ("THF") was cooled to 5°C and 5 g (26 mmol.) 3-bromo-1, 1, 1-trifluoroacetone was added

5   dropwise. The reaction mixture was allowed to warm up to room temperature and was stirred for 3 hours. The reaction mixture was then filtered and the precipitate washed with THF. The filtrate and washings were combined and evaporated. The residue was separated on a column with Silicagel (eluent chloroform – methanol 15:1). Fractions with 3-(4-nitro-phenylthio)-1, 1, 1-trifluoropropan-2-one were combined and evaporated.

10   In step (b), the yield from step (a) was added to a cooled solution of 1 g (15 mmol.) potassium cyanide in water (5 mL) at a rate that maintained temperature of the reaction mixture below 5°C. The mixture was cooled to 0°C and 3.4 mL 25% sulfuric acid was added dropwise while the temperature was kept below 5°C. The reaction mixture was warmed to room temperature and stirred for 20 hours. The reaction mixture

15   was diluted with water (50 mL) and extracted with ether (3 x 150 mL). Combined ether extracts were washed with saturated sodium bicarbonate solution, brine, and dried over sodium sulfate. Solvent was evaporated and 3-(4-nitro-phenylthio)-1,1,1-trifluoropropan-2-one cyanohydrin was obtained as an yellow oil, which solidified in high vacuum.

In step (c), the yield from step (b) was mixed with 20 mL of a concentrated

20   hydrochloric acid – glacial acetic acid (6:1) mixture. The mixture was heated to reflux with vigorous stirring for 20 hours, then cooled to room temperature, diluted with water (100 mL), and extracted with ether (4 x 100 mL). Ether extracts were combined and washed with saturated sodium bicarbonate solution. The aqueous phase was acidified with hydrochloric acid to pH 1 and extracted with ether (4 x 150 mL). Ether extracts

25   were combined, dried over MgSO$_4$, filtered, evaporated, and dried in high vacuum. The resulting oil crystallized after stirring with ligroin. The product, 2-hydroxy-2-(trifluoromethyl)-3-(3-nitro-phenylthio)propionic acid, was filtered and dried in high vacuum.

In step (d), 1.36 g (6 mmol) tin (II) chloride dihydrate was dissolved in 2

30   mL concentrated hydrochloric acid and cooled to 5°C. 0.6 g (2 mmol.) of the yield from step (c) was dissolved in methanol (2 mL) and added dropwise to the reaction flask. The

-36-

reaction mixture was stirred at room temperature for 24 hours. The reaction mixture was evaporated and used for the next reaction as an oil without further purification.

In step (e), the yield from step (d) was dissolved in 25 mL anhydrous acetonitrile and transferred to a reaction flask containing 1 g anhydrous calcium carbonate. 0.1 mL (1.2 mmol.) chloroacetylchloride or acetyl chloride (X = H or Cl) was added slowly and the reaction mixture stirred for 48 hours. The reaction mixture was evaporated and separated by column chromatography (Silicagel, methylene chloride-ethyl acetate 95:5).

In step (f), the yield from step (e) was dissolved in 9 mL anhydrous dimethylacetamide and cooled to -15°C. 0.1 mL (1.5 mmol.) thionyl chloride was added slowly at a rate that maintained the temperature of the reaction mixture below -10°C. The reaction mixture was stirred for 1 hour and the solution of 206 mg (1 mmol.) of 5-amino-2-nitrobenzotrifluoride in 3 mL anhydrous DMA was added dropwise while keeping temperature below -10°C. The reaction mixture was allowed to warm up to room temperature and then stirred 72 hours, evaporated, diluted with saturated sodium bicarbonate solution, extracted with ether, evaporated, and separated by column chromatography (Silicagel, chlorophorm-methanol 19:1). Compound C-12 or C-14 was recovered from the column.

Optionally, at step (g), compounds C-12 or C-14 were oxidized by peracetic acid to form corresponding sulfoderivatives C-13 or C-15, respectively.

Although the invention has been described in detail for the purpose of illustration, it is understood that such detail is solely for that purpose, and variations can be made therein by those skilled in the art without departing from the spirit and scope of the invention which is defined by the following claims.

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WHAT IS CLAIMED:

1.   A non-steroidal agonist compound having the formula:

where R_1, R_2, and R_3 are the same or different and are a hydrogen, a nitro, a cyano, a carbamoyl, a halogen, a perfluoroalkyl, a haloalkylamido, an isothiocyanate, an azide, a diazocarbonyl, a substituted oxirane, or a ß-chloroethylamine;

R_4 is a hydrogen, an alkyl, or is joined to R_5;

R_5 is a hydrogen, a hydroxy, an alkoxy, an acyloxy, an amino, an alkylamino, a halogen, an alkyl, a haloalkyl, or is joined to R_4;

R_6 is a hydrogen, an alkyl, or a haloalkyl;

A_1 and A_2 are the same or different, and each is a direct link or an alkylene;

X_1 is a halogen, an oxygen, a sulfur, a sulphinyl, a sulphonyl, an amino, an alkylimino, or an alkylene;

R_7 is a hydrogen, a halogen, an alkoxy, a haloalkoxy, an acyloxy, a haloacyloxy, an aryloxy, a thioalkyl, a thioraryl, an amino, an alkylimino, an alkylamido group, a haloalkylamido group, or a phenyl optionally substituted with a halogen, a nitro group, an alkyl, a haloalkyl, a cyano, a hydroxyl, a carboxylic group, an amino, an alkylamino group, a dialkylamino group, a bisalkylamino group, a haloalkylamino group, a dihaloalkylamino group, a bishaloalkylamino group, an acylamido group, a diacylamido group, an alkylacylamido group, a haloacylamido group, a bis(haloacyl)imido group, or an alkylhaloacylamido group.

2.   A non-steroidal agonist compound according to claim 1,

wherein R_1 is CF_3,

R_2 is CN or NO_2,

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R_3 and R_4 are H,

R_5 is OH,

R_6 is CH_3 or CF_3,

A_1 is an alkylene or a direct link,

A_2 is a direct link,

X_1 is CH_2, S, or SO_2, and

R_7 is Br, I, or a phenyl ring optionally substituted with a halogen, a nitro group, an alkyl, a haloalkyl, a cyano, a hydroxyl, a carboxylic group, an amino, an alkylamino group, a dialkylamino group, a bisalkylamino group, a haloalkylamino group, a dihaloalkylamino group, a bishaloalkylamino group, an acylamido group, a diacylamido group, an alkylacylamido group, a haloacylamido group, a bis(haloacyl)imido group, or an alkylhaloacylamido group.

3.   A non-steroidal agonist compound according to claim 2, wherein X_1 is CH_2, R_2 is CN, and R_7 is Br.

4.   A non-steroidal agonist compound according to claim 2, wherein X_1 is CH_2, R_2 is NO_2 and R_7 is Br.

5.   A non-steroidal agonist compound according to claim 2, wherein X_1 is CH_2, R_2 is CN and R_7 is I.

6.   A non-steroidal agonist compound according to claim 2, wherein X_1 is CH_2, R_2 is NO_2 and R_7 is I.

7.   A non-steroidal agonist compound according to claim 2, wherein A_1 is an alkylene,

X_1 is S or SO_2, and

R_7 has the formula:

-39-

wherein R_8 is $COCH_3$, $COCH_2Cl$, or $COCH_2CH_3$, and
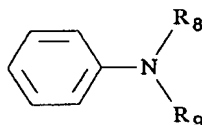
R_9 is H, $COCH_3$, or $COCH_2CH_3$.

8.   A non-steroidal agonist compound according to claim 7, wherein R_8 is $COCH_2Cl$ and R_9 is H.

9.   A non-steroidal agonist compound according to claim 7, wherein R_8 is $COCH_3$ and R_9 is H.

10.   A non-steroidal agonist compound according to claim 7, wherein R_8 and R_9 are $COCH_3$.

11.   A non-steroidal agonist compound according to claim 7, wherein R_8 and R_9 are $COCH_2CH_3$.

12.   A non-steroidal agonist compound according to claim 7, wherein R_8 is $COCH_2CH_3$ and R_9 is H.

13.   A non-steroidal agonist compound according to claim 1, wherein the agonist compound is a substantially pure R enantiomer.

14.   A method of binding a compound to a androgen receptor comprising:

contacting an androgen receptor with a non-steroidal agonist compound under conditions to bind the non-steroidal agonist compound to the androgen receptor.

15.   A method according to claim 14, wherein the non-steroidal agonist compound is a compound having a formula:

where R_1, R_2, and R_3 are the same or different and are a hydrogen, a nitro, a cyano, a

carbamoyl, a halogen, a perfluoroalkyl, a haloalkylamido, an isothiocyanate, an

5   azide, a diazocarbonyl, a substituted oxirane, or a ß-chloroethylamine;

R_4 is a hydrogen, an alkyl, or is joined to R_5;

R_5 is a hydrogen, a hydroxy, an alkoxy, an acyloxy, an amino, an alkylamino,

a halogen, an alkyl, a haloalkyl, or is joined to R_4;

R_6 is a hydrogen, an alkyl, or a haloalkyl;

10   A_1 and A_2 are the same or different, and each is a direct link or an alkylene;

X_1 is a halogen, an oxygen, a sulfur, a sulphinyl, a sulphonyl, an amino, an

alkylimino, or an alkylene;

R_7 is a hydrogen, a halogen, an alkoxy, a haloalkoxy, an acyloxy, a

haloacyloxy, an aryloxy, a thioalkyl, a thioraryl, an amino, an alkylimino, an alkylamido

15   group, a haloalkylamido group, or a phenyl optionally substituted with a halogen, a nitro

group, an alkyl, a haloalkyl, a cyano, a hydroxyl, a carboxylic group, an amino, an

alkylamino group, a dialkylamino group, a bisalkylamino group, a haloalkylamino group, a

dihaloalkylamino group, a bishaloalkylamino group, an acylamido group, a diacylamido

group, an alkylacylamido group, a haloacylamido group, a bis(haloacyl)imido group, or an

20   alkylhaloacylamido group.

16.   A method according to claim 15,

wherein R_1 is CF_3,

R_2 is CN or NO_2,

25   R_3 and R_4 are H,

R_5 is OH,

R_6 is CH_3 or CF_3,

A_1 is an alkylene or a direct link,

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A_2 is a direct link,

X_1 is CH_2, S, or SO_2, and

R_7 is Br, I, or a phenyl ring optionally substituted with a halogen, a nitro group, an alkyl, a haloalkyl, a cyano, a hydroxyl, a carboxylic group, an amino, an alkylamino group, a dialkylamino group, a bisalkylamino group, a haloalkylamino group, a dihaloalkylamino group, a bishaloalkylamino group, an acylamido group, a diacylamido group, an alkylacylamido group, a haloacylamido group, a bis(haloacyl)imido group, or an alkylhaloacylamido group.

17.   A method according to claim 16,

wherein A_1 is an alkylene,

X_1 is S or SO_2, and

R_7 has the formula:
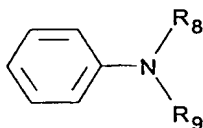
wherein R_8 is $COCH_3$, $COCH_2Cl$, or $COCH_2CH_3$, and

R_9 is H, $COCH_3$, or $COCH_2CH_3$.

18.   A method according to claim 14, wherein the non-steroidal agonist compound is a substantially pure R enantiomer.

19.   A method of suppressing spermatogenesis in a male patient comprising:

contacting an androgen receptor of a male patient with a non-steroidal agonist compound under conditions effective bind the non-steroidal agonist compound to the androgen receptor and suppress spermatogenesis.

20.   A method according to claim 19, wherein the non-steroidal agonist compound is a compound having a formula:

where R_1, R_2, and R_3 are the same or different and are a hydrogen, a nitro, a cyano, a

5   carbamoyl, a halogen, a perfluoroalkyl, a haloalkylamido, an isothiocyanate, an

azide, a diazocarbonyl, a substituted oxirane, or a ß-chloroethylamine;

           R_4 is a hydrogen, an alkyl, or is joined to R_5;

           R_5 is a hydrogen, a hydroxy, an alkoxy, an acyloxy, an amino, an alkylamino,

a halogen, an alkyl, a haloalkyl, or is joined to R_4;

10   R_6 is a hydrogen, an alkyl, or a haloalkyl;

           A_1 and A_2 are the same or different, and each is a direct link or an alkylene;

           X_1 is a halogen, an oxygen, a sulfur, a sulphinyl, a sulphonyl, an amino, an

alkylimino, or an alkylene;

           R_7 is a hydrogen, a halogen, an alkoxy, a haloalkoxy, an acyloxy, a

15   haloacyloxy, an aryloxy, a thioalkyl, a thioraryl, an amino, an alkylimino, an alkylamido

group, a haloalkylamido group, or a phenyl optionally substituted with a halogen, a nitro

group, an alkyl, a haloalkyl, a cyano, a hydroxyl, a carboxylic group, an amino, an

alkylamino group, a dialkylamino group, a bisalkylamino group, a haloalkylamino group, a

dihaloalkylamino group, a bishaloalkylamino group, an acylamido group, a diacylamido

20   group, an alkylacylamido group, a haloacylamido group, a bis(haloacyl)imido group, or an

alkylhaloacylamido group.

           ·21.   A method according to claim 20,

           wherein R_1 is CF_3,

25   R_2 is CN or NO_2,

           R_3 and R_4 are H,

           R_5 is OH,

           R_6 is CH_3 or CF_3,

-43-

A_1 is an alkylene or a direct link,

A_2 is a direct link,

X_1 is CH_2, S, or SO_2, and

R_7 is Br, I, or a phenyl ring optionally substituted with a halogen, a nitro group, an alkyl, a haloalkyl, a cyano, a hydroxyl, a carboxylic group, an amino, an alkylamino group, a dialkylamino group, a bisalkylamino group, a haloalkylamino group, a dihaloalkylamino group, a bishaloalkylamino group, an acylamido group, a diacylamido group, an alkylacylamido group, a haloacylamido group, a bis(haloacyl)imido group, or an alkylhaloacylamido group.

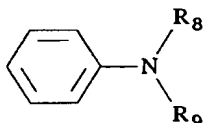22.   A method according to claim 21,

wherein A_1 is an alkylene,

X_1 is S or SO_2, and

R_7 has the formula:

wherein R_8 is $COCH_3$, $COCH_2Cl$, or $COCH_2CH_3$, and

R_9 is H, $COCH_3$, or $COCH_2CH_3$.

23.   A method according to claim 19, wherein the non-steroidal agonist compound is a substantially pure R enantiomer.

24.   A method of hormone therapy comprising:

contacting an androgen receptor of a male patient with a non-steroidal agonist compound under conditions effective to bind the non-steroidal agonist compound to the androgen receptor and effect a change in an androgen-dependent condition.

-44-

25.   A method according to claim 24, wherein the non-steroidal agonist compound is a compound having a formula:

5
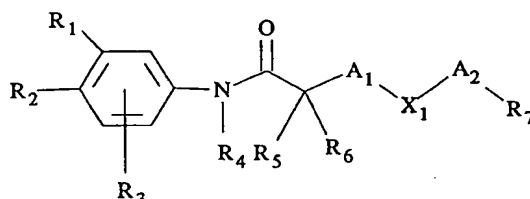
where R_1, R_2, and R_3 are the same or different and are a hydrogen, a nitro, a cyano, a carbamoyl, a halogen, a perfluoroalkyl, a haloalkylamido, an isothiocyanate, an azide, a diazocarbonyl, a substituted oxirane, or a ß-chloroethylamine;

R4 is a hydrogen, an alkyl, or is joined to R5;

10   R5 is a hydrogen, a hydroxy, an alkoxy, an acyloxy, an amino, an alkylamino, a halogen, an alkyl, a haloalkyl, or is joined to R4;

R6 is a hydrogen, an alkyl, or a haloalkyl;

A1 and A2 are the same or different, and each is a direct link or an alkylene;

X1 is a halogen, an oxygen, a sulfur, a sulphinyl, a sulphonyl, an amino, an

15   alkylimino, or an alkylene;

R7 is a hydrogen, a halogen, an alkoxy, a haloalkoxy, an acyloxy, a haloacyloxy, an aryloxy, a thioalkyl, a thioraryl, an amino, an alkylimino, an alkylamido group, a haloalkylamido group, or a phenyl optionally substituted with a halogen, a nitro group, an alkyl, a haloalkyl, a cyano, a hydroxyl, a carboxylic group, an amino, an

20   alkylamino group, a dialkylamino group, a bisalkylamino group, a haloalkylamino group, a dihaloalkylamino group, a bishaloalkylamino group, an acylamido group, a diacylamido group, an alkylacylamido group, a haloacylamido group, a bis(haloacyl)imido group, or an alkylhaloacylamido group.

25   26.   A method according to claim 25,

wherein R_1 is CF_3,

R_2 is CN or NO_2,

R_3 and R_4 are H,

-45-

R_5 is OH,

R_6 is CH_3 or CF_3,

A_1 is an alkylene or a direct link,

A_2 is a direct link,

X_1 is CH_2, S, or SO_2, and

R_7 is Br, I, or a phenyl ring optionally substituted with a halogen, a nitro group, an alkyl, a haloalkyl, a cyano, a hydroxyl, a carboxylic group, an amino, an alkylamino group, a dialkylamino group, a bisalkylamino group, a haloalkylamino group, a dihaloalkylamino group, a bishaloalkylamino group, an acylamido group, a diacylamido group, an alkylacylamido group, a haloacylamido group, a bis(haloacyl)imido group, or an alkylhaloacylamido group.

27.   A method according to claim 26,

wherein A_1 is an alkylene,

X_1 is S or SO_2, and

R_7 has the formula:

wherein R_8 is $COCH_3$, $COCH_2Cl$, or $COCH_2CH_3$, and

R_9 is H, $COCH_3$, or $COCH_2CH_3$.

28.   A method according to claim 24, wherein the non-steroidal agonist compound is a substantially pure R enantiomer.

29.   A method according to claim 24, wherein the androgen-dependent condition is selected from a group consisting of hypogonadism, sarcopenia, erythropoiesis, and osteoporosis.

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30.   A composition comprising:

a non-steroidal agonist compound and a pharmaceutically acceptable carrier;

wherein the non-steroidal agonist compound has the formula:
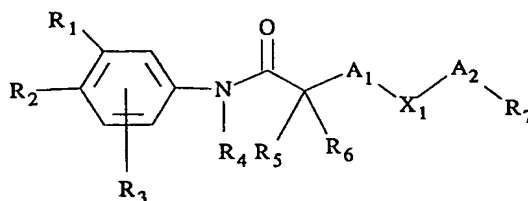
5

where R_1, R_2, and R_3 are the same or different and are a hydrogen, a nitro, a cyano, a

carbamoyl, a halogen, a perfluoroalkyl, a haloalkylamido, an isothiocyanate, an

azide, a diazocarbonyl, a substituted oxirane, or a ß-chloroethylamine;

10   R_4 is a hydrogen, an alkyl, or is joined to R_5;

R_5 is a hydrogen, a hydroxy, an alkoxy, an acyloxy, an amino, an alkylamino,

a halogen, an alkyl, a haloalkyl, or is joined to R_4;

R_6 is a hydrogen, an alkyl, or a haloalkyl;

A_1 and A_2 are the same or different, and each is a direct link or an alkylene;

15   X_1 is a halogen, an oxygen, a sulfur, a sulphinyl, a sulphonyl, an amino, an

alkylimino, or an alkylene;

R_7 is a hydrogen, a halogen, an alkoxy, a haloalkoxy, an acyloxy, a

haloacyloxy, an aryloxy, a thioalkyl, a thioaryl, an amino, an alkylimino, an alkylamido

group, a haloalkylamido group, or a phenyl optionally substituted with a halogen, a nitro

20   group, an alkyl, a haloalkyl, a cyano, a hydroxyl, a carboxylic group, an amino, an

alkylamino group, a dialkylamino group, a bisalkylamino group, a haloalkylamino group, a

dihaloalkylamino group, a bishaloalkylamino group, an acylamido group, a diacylamido

group, an alkylacylamido group, a haloacylamido group, a bis(haloacyl)imido group, or an

alkylhaloacylamido group.

25

31.   A composition according to claim 30,

wherein R_1 is CF_3,

R_2 is CN or NO_2,

R_2 is CN or NO_2,

R_3 and R_4 are H,

R_5 is OH,

R_6 is CH_3 or CF_3,

A_1 is an alkylene or a direct link,

A_2 is a direct link,

X_1 is CH_2, S, or SO_2, and

R_7 is Br, I, or a phenyl ring optionally substituted with a halogen, a nitro group, an alkyl, a haloalkyl, a cyano, a hydroxyl, a carboxylic group, an amino, an alkylamino group, a dialkylamino group, a bisalkylamino group, a haloalkylamino group, a dihaloalkylamino group, a bishaloalkylamino group, an acylamido group, a diacylamido group, an alkylacylamido group, a haloacylamido group, a bis(haloacyl)imido group, or an alkylhaloacylamido group.
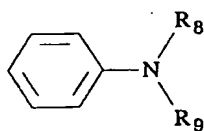

32.   A composition according to claim 31,

wherein A_1 is an alkylene,

X_1 is S or SO_2, and

R_7 has the formula:

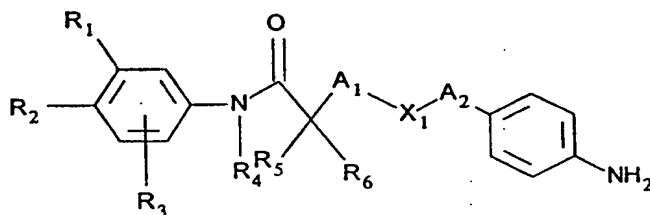wherein R_8 is $COCH_3$, $COCH_2Cl$, or $COCH_2CH_3$, and

R_9 is H, $COCH_3$, or $COCH_2CH_3$.

33.   A composition according to claim 30, wherein the non-steroidal agonist compound is a substantially pure R enantiomer.

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34.   A method of producing a non-steroidal agonist compound, said method comprising:

providing an intermediate compound having the formula:

where R_1, R_2, and R_3 are the same or different and are a hydrogen, a nitro, a cyano, a carbamoyl, a halogen, a perfluoroalkyl, a haloalkylamido, an isothiocyanate, an azide, a diazocarbonyl, a substituted oxirane, or a ß-chloroethylamine,

R_4 is a hydrogen, an alkyl, or is joined to R_5,

R_5 is a hydrogen, a hydroxy, an alkoxy, an acyloxy, an amino, an alkylamino, a halogen, an alkyl, a haloalkyl, or is joined to R_4,

R_6 is a hydrogen, an alkyl, or a haloalkyl,

A_1 and A_2 are the same or different, and each is a direct link or an alkylene, and

X_1 is a halogen, an oxygen, a sulfur, a sulphinyl, a sulphonyl, an amino, an alkylimino, or an alkylene,

providing an acyl halide or a haloacyl halide; and

reacting the intermediate compound with the acyl halide or the haloacyl halide to produce a non-steroidal agonist compound having the formula:
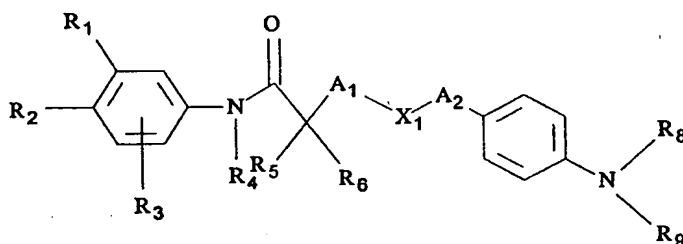
-49-

where R_1, R_2, R_3, R_4, R_5, R_6, A_1, A_2, and X_1 are as defined above, and R_8 and R_9 are hydrogen, an acyl group, or a haloacyl group.

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) :Please See Extra Sheet.
US CL :Please See Extra Sheet.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
U.S. : 514/256, 307, 311, 346, 357, 359, 361, 363, 394, 398, 400, 415, 424, 427, 438, 443, 445, 469, 470, 471, 522, 546, 618, 625, 841

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS-ONLINE, APS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4,636,505 A (TUCKER) 13 January 1987, see the entire document.	1-34

☐ Further documents are listed in the continuation of Box C.   ☐ See patent family annex.

	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance		
"E"	earlier document published on or after the international filing date	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed	"&"	document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 AUGUST 1998	0 2 OCT 1998
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer KEVIN E. WEDDINGTON
Facsimile No. (703) 305-3230	Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)★

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (6):

A61K 31/505, 31/47, 31/44, 31/415, 31/405, 31/40, 31/38, 31/34, 31/275, 31/22, 31/165

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

514/256, 307, 311, 346, 357, 359, 361, 363, 394, 398, 400, 415, 424, 427, 438, 443, 445, 469, 470, 471, 522, 546, 618, 625, 841